Patent
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Bookser *et al.*	
Serial No.: 09/801,933	Group Art Unit: 1624
Filed: March 7, 2001	Examiner: McKenzie, T.
Title: **NOVEL ARYL FRUCTOSE-1,6-BISPHOSPHATASE INHIBITORS**	

Mail Stop RCE
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MARK D. ERION PURSUANT TO 37 C.F.R. § 1.132

I, Mark D. Erion, a citizen of the United States, declare and say that:

1. I have a Ph.D. in synthetic organic chemistry from Cornell University, and I have over 16 years experience in the pharmaceutical industry. I am currently the Executive Vice President of Research & Development at Metabasis Therapeutics, Inc. in San Diego, CA. As such, I am responsible for all discovery research and development. I have developed prodrug technology that enables the delivery of phophonic acid containing drugs to the liver. I also headed the R&D team responsible for the identification of clinical candidates for diabetes, hepatitis B, and hepatocellular carcinoma. Prior to my being a co-founder of Metabasis Therapeutics in 1997, I was the Division Vice President of Research at Gensia, Inc. in San Diego, CA. Prior to joining Gensia in 1991, I was a group leader at Ciba-Geigy where I directed a team in the area of protein engineering at Ciba-Geigy's Central Research Laboratories in Switzerland. I have over 80 publications and 25 U.S. patents. Through my work, I have had extensive experience in the area of prodrugs.

2. I have reviewed the specification, the pending claims, and the office action mailed November 25, 2002.

3. It is my understanding that the Examiner has found that claims 1-6 and 8-36 are indefinite and not enabled because of the use of the term "prodrug." In particular, it is my understanding

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(37 C.F.R. §1.8)

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that the Examiner finds the structures of the claimed prodrugs to be uncertain. The Examiner believes that one cannot determine what compounds are claimed.

4. Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art. As defined at pp. 10-11 of the specification a prodrug is a compound that undergoes a chemical modification to form a biologically active molecule r a precursor to the biologically active drug. There are many commonly known prodrugs. For example, a compound may have a free hydroxyl group on it. A common prodrug of a hydroxyl is an ester. Esters are often quickly broken down within the body to produce the compound with the free hydroxyl. In this example, the ester is the prodrug. In general, each functional group, e.g. hydroxyl, thiol, amine, carboxylic acid, has a set of well described prodrugs that have proven useful for masking the functional group in a manner that enables improved oral bioavailability, improved pharmacokinetics, improved distribution, or other properties readily observable during testing in animals and man. It is well recognized that based on the functional group and the reasons for using a prodrug, one skilled in the art can generally choose a prodrug strategy that is successful without undue experimentation.

5. The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 2000. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation.

6. In some cases, the mechanism for activation of the prodrug is well understood making it even easier to test for conversion to the biologically active drug. For instance, an article in *Pharm. Res.* (Exhibit 1) reveals that concentrations of the prodrug bis(POM)-PMEA and its metabolites mono(POM)-PMEA and PMEA were determined using a reversed-phase HPLC method. The activation of the prodrug was confirmed by incubating the prodrug with carboxylesterase.

7. In addition to these analytical methods, prodrugs that are converted to the biologically active drug are readily evaluated by using *in vitro* or *in vivo* assays to demonstrate a biological response. As noted in the specification, the claimed compounds include FBPase inhibitors, pharmaceutically acceptable salts and prodrugs. (e.g. p. 3) FBPase is an enzyme in the gluconeogenesis pathway and is active in rat hepatocytes. As described in Example E (p. 137), one can readily determine if a prodrug is converted to the biologically active drug by monitoring glucose production in primary rat hepatocytes.

8. I also note that the specification provides adequate detail to a person of ordinary skill in the art in order to allow them to prepare the prodrugs of the current invention. A person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 98-108 of the specification and by the definition of the term "prodrug" at pp. 10-11 of the specification.

9. I have also reviewed the references discussed by the Examiner on pp. 10-14 of the Office Action, including Sanchez (*J. Med. Chem.*), Serafinowska (*J. Med. Chem.*), Bundgaard (*J. Med. Chem.*), and Shan (*J. Pharmaceutical Sci.*). In my view these references demonstrate that prodrug

preparation is routine. The testing indicated by these references is routine and would not be considered undue.

10. In view of the specification, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of this invention.

5/23/03
Date

Mark D. Erion, Ph.D.